New methods for the enantiomeric excess determination using NMR

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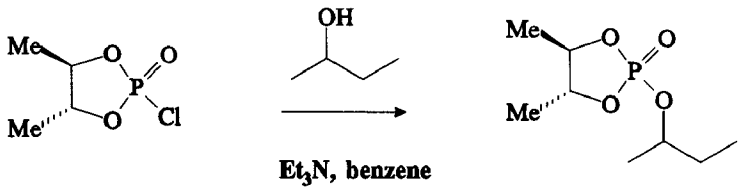
CHAPTER 3

The use of chiral diazaphospholidines as agents for the enantiomeric excess determination of amines and alcohols

3.1 *Trivalent phosphorus containing chiral derivatizing agents for the enantiomeric excess determination*

One of the most attractive nuclei to use in NMR analysis of chiral materials undoubtedly is the phosphorus-31 nucleus. The advantages of using ^{31}P NMR are clear: usually the shift dispersion is large and relatively simple spectra are obtained when broad-band decoupling is used. Furthermore, the ^{31}P nucleus is very sensitive towards (small) structural changes and can easily be measured[1]. Knowing this, it is not surprising that a number of methods have been developed in the field of enantiomeric excess determination of amines, alcohols and derivatives of amino acids using ^{31}P NMR spectroscopic techniques[#]. Nearly all known methods are based upon the use of derivatizing agents, containing a *pentavalent* phosphorus atom[2]. Typically, this means that a chiral phosphoric acid chloride is allowed to react with the substrate under well defined conditions, affording diastereomeric products which can be analyzed[3] (Scheme **3.1**).



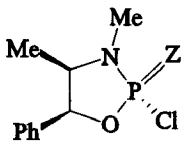
3.1 **3.2**

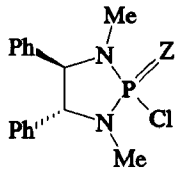
Scheme 3.1 A typical example of a chiral pentavalent phosphorus derivatizing agent

The phosphates obtained give $\Delta\delta$ values (^{31}P NMR) that are not very large, typically between 0 and 0.13 ppm. In the *C-2* symmetrical chlorodioxaphospholane **3.1**, the phosphorus atom is not chiral so that inversion or retention of configuration at phosphorus during the displacement of chloride by an enantio-pure alcohol yields the same diastereomer **3.2**. The $\Delta\delta$ values can be slightly increased by reducing the electrophilicity of the pentavalent phosphorus atom, *e.g.* by replacing one or both oxygen atoms by nitrogen atoms, as in **3.3** and **3.4** (Scheme **3.2**). It should, however, be noted that more

[#] See reference 2 and Chapter 1 for a review concerning phosphorus containing agents for the enantiomeric excess determination.

forcing conditions are required to make these agents react, for example by the use of a stronger base (NaH), higher temperatures (refluxing THF) and prolonged reaction times[4,5]. Moreover, the low reactivity towards *e.g.* tertiary alcohols and other sterically hindered systems, limits their use in the analysis of enantiomeric composition.

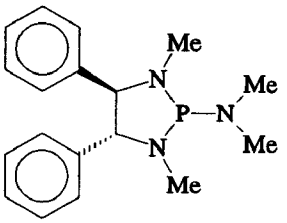


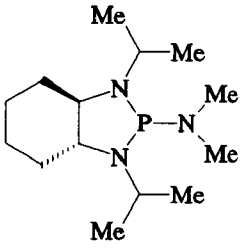


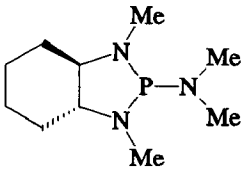
3.3 **3.4** **Z= O, S**

Scheme 3.2 Modified pentavalent phosphorus derivatizing agents 3.3 and 3.4

The highest reactivity in combination with large ^{31}P NMR $\Delta\delta$ values for the diastereomeric adducts can be obtained when chiral *trivalent* phosphorus containing reagents, as developed by Alexakis and co-workers[6], are used (Scheme **3.3**).



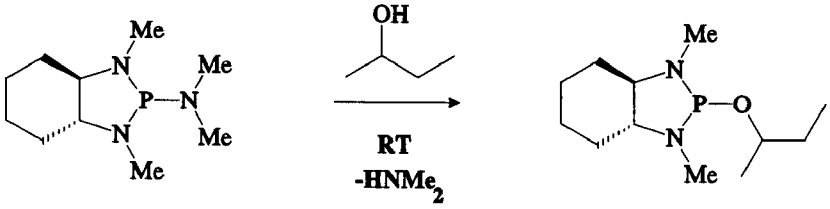




3.5 **3.6** **3.7**

Scheme 3.3 Three trivalent phosphorus containing chiral derivatizing agents

These reagents form derivatives with primary, secondary and tertiary alcohols even at room temperature, simply by stirring with the substrate of interest in toluene without the need of additional reagents. The exocylic P-N bond of these aminophosphines is easily cleaved by alcohols and amines[7,8], affording the (diastereomeric) products **3.8** as is shown for sec-butanol in Scheme **3.4**. A large variety of chiral alcohols could be analyzed with *e.g.* reagent **3.7**, to give $\Delta\delta$ values of between 0.5 and 12.1 ppm (!)[6] for the diastereomeric products using ^{31}P NMR. Furthermore, these reagents are easily prepared by an amine exchange reaction with $P(NMe_2)_3$ (*H*exa*M*ethyl*P*hosphorus*T*riamide, HMPT) and the desired chiral bisamine which is, though expensive, commercially available. These reagents are, furthermore, reported to be stable for months in an inert atmosphere, but they are very sensitive to moisture[6,9].



3.7 3.8

Scheme 3.4 The reaction of racemic sec-butanol with derivatizing agent 3.7

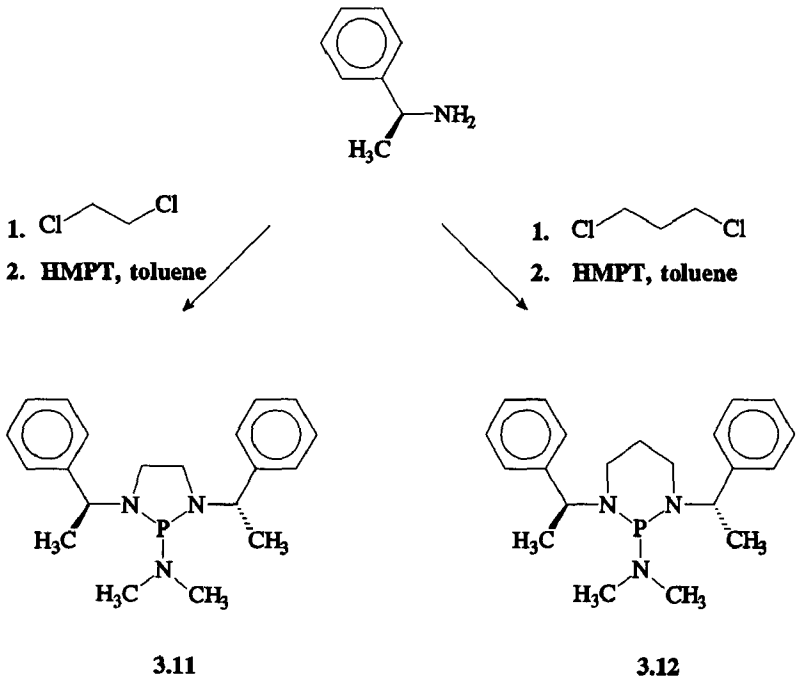
Being aware of the advantages using phosphorus containing derivatizing agents in the enantiomeric excess determination of amines, alcohols, amino alcohols and amino acids (see also Chapters 1, 4 and 5), it seemed obvious that modified, trivalent phosphorus containing compounds might be of great interest, not only for the enantiomeric excess determination itself, but also to gather more insight in the relationship between the obtained chemical shift differences $\Delta\delta$ (in the decoupled ^{31}P NMR spectra) and the structure of the phosphorus containing diastereomeric products[1,10,11].

3.2 *The synthesis of new, modified trivalent diazaphospholidines, oxazaphospholidines and dioxophospholidines.*

Although the results in the enantiomeric excess determination as obtained by the derivatizing agents **3.5**, **3.6** and **3.7** developed by Alexakis and co-workers[6] can hardly be improved, the *trivalent phosphorus* method is not tolerant towards (traces of) water, making this method in the field of enantiomeric excess determination of *amino acids* of little or no use. Besides, the bisamines as used by Alexakis are relatively expensive and only available after tedious preparation. Furthermore, reagent **3.7** is based upon a system that contains two annulated ring systems with considerable ring strain, making agent **3.7** not very stable towards reagents or solvents (like water).
Products **3.8**, obtained on reaction of **3.7** with nucleophiles, appear not to be very stable either.
Therefore, it would be of considerable interest when derivatives were available that are: (a) based upon cheaper and more easily available bisamines and (b), built in such way that the reactivity towards nucleophiles is more balanced, so that water is acceptable as (co)-solvent and amino acids still react. In this way it should be possible to study the scope and limitations as reagent for the determination of the enantiomeric excess and obtain insight into the factors that govern the diastereomeric peak separation in the decoupled ^{31}P NMR spectra.

3.2.1 *About diazaphospholidines*

An elegant way to meet both requirements described above, is the use of a bis-amine, that is based upon the very cheap and enantiomerically pure (*S*)-α-phenylethylamine in the formation of a diazaphospholidine.



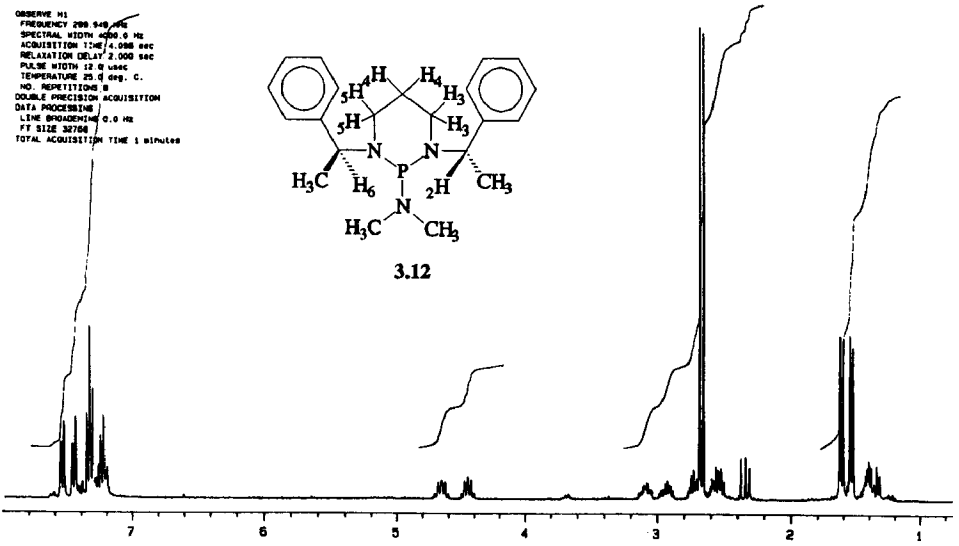
3.11 **3.12**

Scheme 3.5 Synthesis of the derivatizing agents 3.11 and 3.12

The reaction of (*S*)-α-phenylethylamine with either 1,2-dichloroethane or 1,3-dichloropropane without solvent (neat) affords bisamines **3.9** and **3.10** (not shown) in good yield (62 and 84% respectively)[12]. The subsequent amine exchange reaction with HMPT in dry toluene or benzene under acidic catalysis (dry NH_4Cl) affords diazaphospholidines **3.11** and **3.12** in nearly quantitative yield (Scheme **3.5**). *Attempts to purify these materials even on a small scale by means of distillation under reduced pressure resulted in violent explosions.* A reasonable alternative for the purification is column chromatography using a small Al_2O_3 column under nitrogen, affording the nearly pure products as determined by the ^1H NMR. These materials are sufficiently pure for use in the enantiomeric excess determination.

The ^1H NMR spectra of **3.11** and **3.12** are complex, showing large shift differences, *e.g.* for the protons of the 5 or 6 ring system. The shifts arise from the influence of the electron density located on the phosphorus nucleus (free electron pair). Due to extensive $^3J_{P-H}$ coupling and the fact that all the CH_2 protons in this system are nonequivalent, the spectra show complex coupling patterns (Figures **3.1** and **3.2**).

The ^{1}H NMR of crude **3.12** clearly shows two multiplets at δ 4.31 and δ 4.45 ppm, belonging to the exocyclic protons (2 and 6). Both are located near the free electron pairs at the ring nitrogen atoms and show a large shift compared to the free ligand (typically Δδ 0.4 ppm).



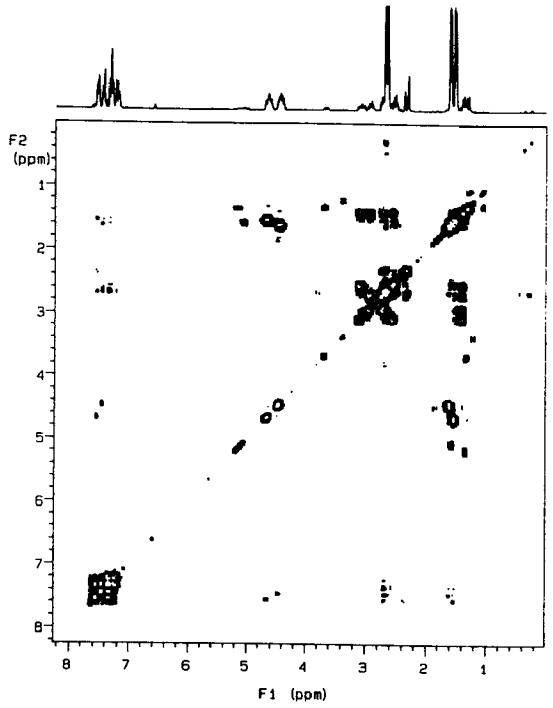
3.12

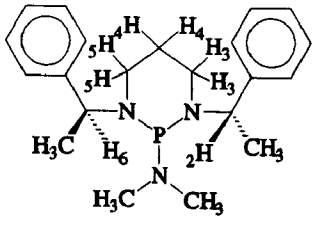
Figure 3.1 *The ^{1}H NMR spectrum of crude 3.12 recorded in $CDCl_3$ at [L]= 0.1 M*

The protons $\underline{4}^{ax}$ and $\underline{4}^{eq}$ are located around δ 1.51 ppm, and the axial protons 3 and 5 are located at δ 2.53 and δ 2.62 ppm, respectively. The equatorial protons 3 and 5 are shifted to δ 2.90 and δ 3.10 ppm, probably because they are situated in the vicinity of the electron density which is located on the phosphorus atom (free electron pair).

From the COSY spectrum (Figure **3.2**) the relationship between $\underline{3}^{ax}$ and $\underline{3}^{eq}$ as well as the relationship between $\underline{5}^{ax}$ and $\underline{5}^{eq}$ is easily revealed, although they are significantly shifted due to ring current of the aromatic ring systems. The NOESY spectrum (Figure **3.2**) is in agreement with the assignments as proposed, showing no interaction for the equatorially positioned NMe_2 group.

Surprisingly, no evidence for π–stacking of the aromatic systems was found. For further assignment, the reader is referred to the experimental section. Furthermore, the observed shifts are rather sensitive towards the solvent used. For the methyl signals (at δ 1.51 ppm), Δδ values of 0.25 ppm were found upon changing the solvent from benzene to chloroform. These shifts show no temperature dependence (in benzene) over the temperature range 20–80 °C, indicating that the conformational freedom is very limited, so that conformational changes do not contribute to the observed phenomena. The spectral behavior of reagent **3.11** is not discussed in greater detail here, but comparable shifts are found. It is important to note that **3.11** and **3.12** are stable in air and reasonably insensitive towards moisture, in contrast to the derivatizing agents used by Alexakis[5,6]. Reaction to provide the diastereomeric products nearly always proceeds quantitatively without side product





3.12

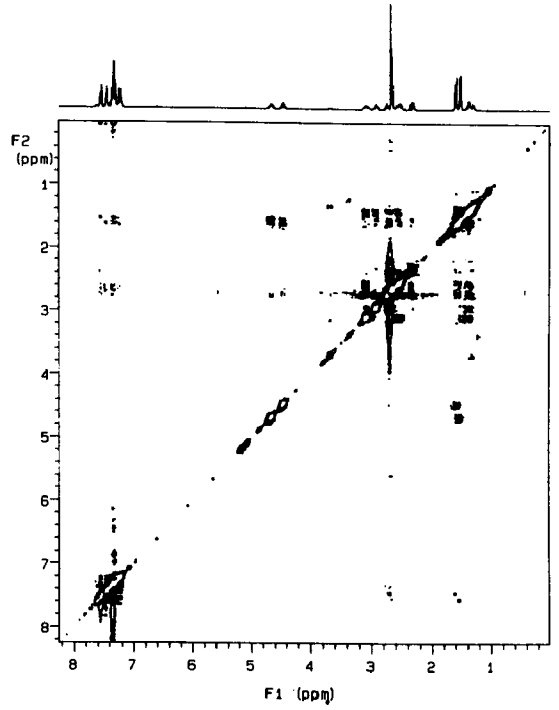
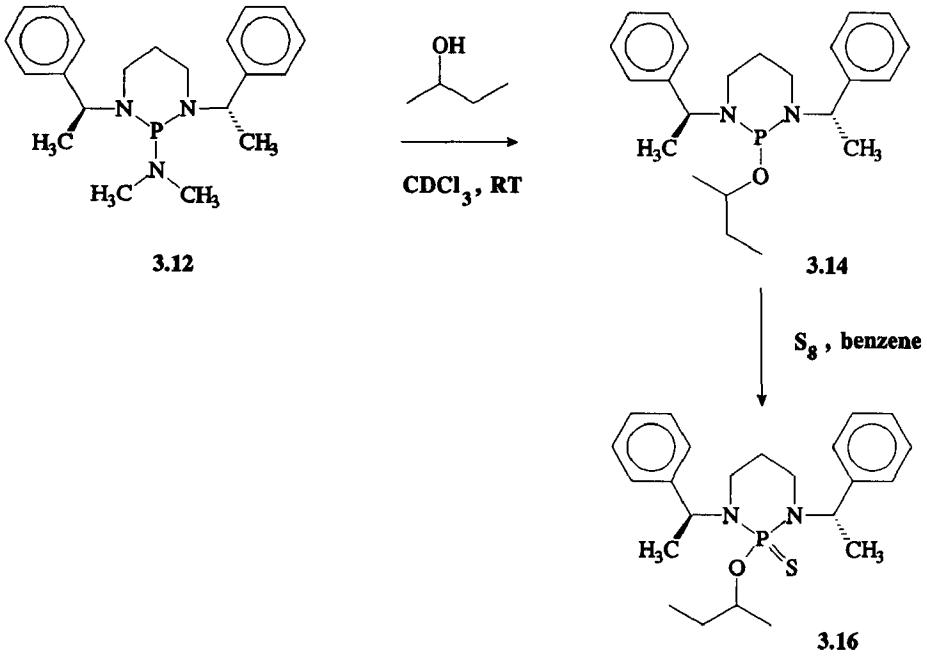


Figure 3.2 COSY and NOESY spectra of crude 3.12 recorded in C_6D_6 at [L]= 0.1 M

formation (except for certain entries that will be discussed in greater detail). The reagents **3.11** and **3.12** can be stored as such, or as a solution in benzene or chloroform for at least six months without decomposition.

3.2.2 *The use of diazaphospholidines 3.11 and 3.12 in the enantiomeric excess determination: scope and limitations*

As with reagent **3.7**, the exocyclic P–N bond of **3.11** and **3.12** is readily cleaved by various nucleophiles[9], including alcohols, amines and thiols. The derivatizing procedure involves the mixing of the substrate of interest (typically 0.1 mmole) with a slight excess (1.1 equivalent) of derivative **3.11** or **3.12** in the solvent of choice ($CDCl_3$ or C_6D_6, 1.5 mL), followed by stirring at room temperature until dimethylamine is no longer evolved (this can easily be checked with pH indicator). Normally, the reactions take about 1–8 h for completion.



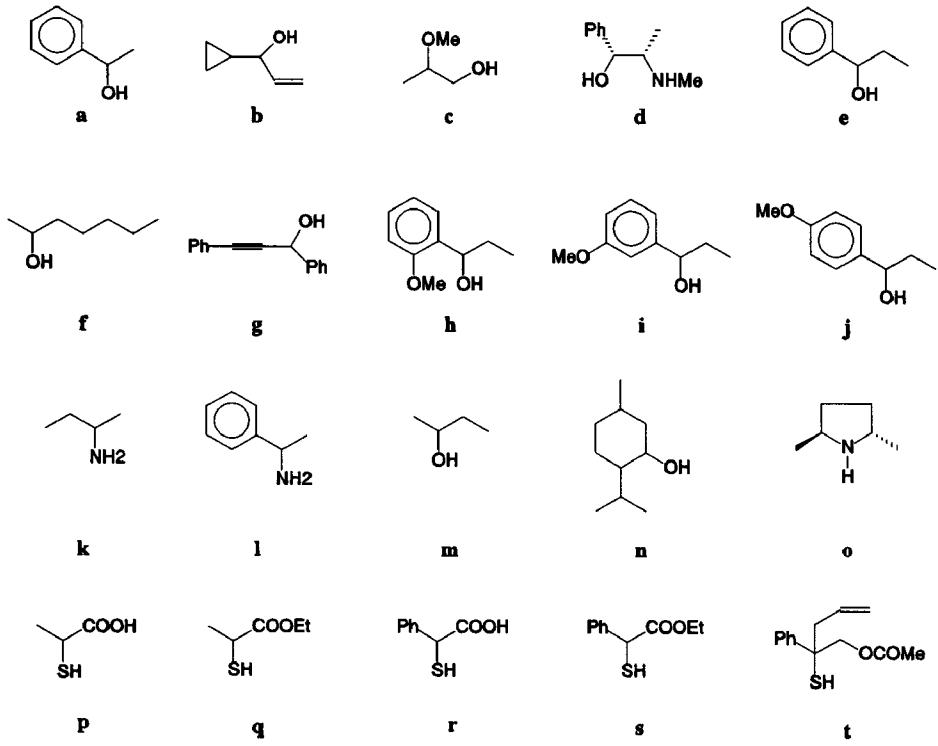
3.12 **3.14** **3.16**

Scheme 3.6 Reaction of 3.12 with racemic sec-butanol. Subsequent reaction with S_8 renders the compounds 3.14 into thiophosphoramidate 3.16

Subsequent ^{31}P or ^{1}H NMR analysis provides the diastereomeric ratios immediately. Since the diastereomeric derivatives **3.13** and **3.14** of reagents **3.11** and **3.12** (Scheme **3.6** and **3.11**) are not stable to TLC or GC analysis, the conversion was easily monitored converting **3.13** or **3.14** with sulfur (S_8) powder into the more stable thio derivatives **3.15** and **3.16**, analogous to the method described by Alexakis and co-workers[5,6]. The

thiophosphoramidates **3.15** and **3.16** are formed instantaneously and these air stable products are easily analyzed using TLC or GC techniques[6,13].

Reagents **3.11** and **3.12** were evaluated using a variety of racemic chiral alcohols, amines, amino alcohols, α–thiol acids and α–thiol acid esters and even some *free* amino acids[#] as shown in Scheme **3.7** and Tables **3.1** and **3.2**. Reactions took place with the nucleophiles tested so far within 8 h, regardless their steric bulk or structure. The obtained diastereomeric ratios for racemic substrates were all 50:50 within the experimental limits (2 %). No signs of kinetic resolution were found, not even when reactions were monitored during the complete course of the conversion. The results obtained with reagent **3.12** are collected in Table **3.1**, the indexes referring to Scheme **3.7**.



Scheme 3.7 Representative alcohols, amines and thio acid derivatives used for the e.e. determination. The indexes are also used in Table 3.1 and 3.2

The obtained Δδ values using ^{31}P NMR are typically in the order of 0.08 ppm (for **c**) to 4.52 ppm (for **d**), although larger shift differences have been observed. Usually, two nicely separated singlets are observed between δ 115–125 ppm for derivatized alcohols, between δ 90–100 ppm for derivatized amines and between δ 140–155 ppm for the thiol acid

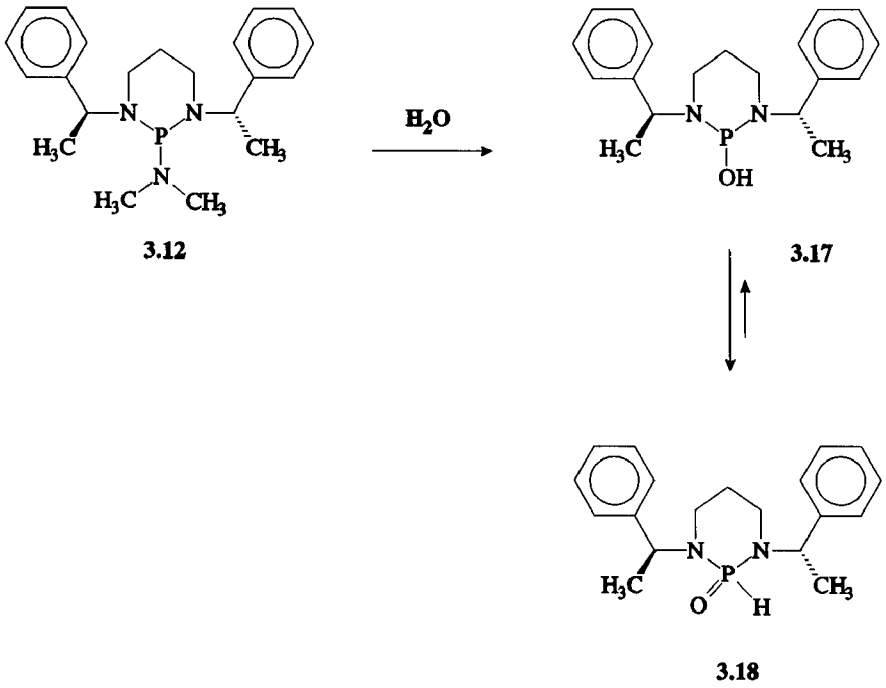
[#] Scheme **3.9** and the Tables **3.1** and **3.2** contain only a part of the analyzed substrates.

Substrate	δ (ppm)	$\Delta\delta$ (ppm)	ratio
a	121.52	1.38	50:50
b	120.60	0.15	50:50
c	116.25	0.08	49.5:50.5
d	121.70	4.52	50:50
e	118.53	3.69	50:50
f	120.60	1.10	49.4:50.6
g	118.05	4.62	49.5:50.5[a]
h	120.40	2.86	50:50
i	121.66	3.62	50:50
j	118.79	3.47	50:50
k	93.40	0.26	50:50
l	93.07	2.46	50:50
m	122.81	2.73	49.4:50.6
n	118.70	1.69	49.5:50.5
o	98.50	1.31	49.5:50.5
p	145.79	2.30	43:57[b]
q	152.47	0.23	42:58[b]
r	149.28	0.19	49.5:50.5
s	152.71	1.09	49.5:50.5
t	144.29	0.53	29.5:70.5[c]

Table 3.1 *^{31}P NMR data of derivatives of **3.12** and racemic alcohols, amines and α-thiol acids and the corresponding esters recorded in $CDCl_3$ [L]= 0.1 M.*
a) An additional signal was observed at δ 21.1 ppm, see text for explanation.
b) Enriched compounds were used, e.e. unknown.
c) The e.e. determined by GC analysis was 41%; unpublished results, Hof, R.P., Kellogg, R.M., manuscript in preparation.

adducts of **3.12** (for examples, see Chapter 3.2.3). It is clearly shown that, for the alcohols used, reagent **3.12** gives the largest shift differences ($\Delta\delta$) with alcohols that contain an aromatic group, as for **a** (1.38 ppm), **d** (4.52 ppm), **e** (3.69 ppm) and the series **h–j** (2.86–3.62 ppm). Also when bulky alcohols are used, relatively large $\Delta\delta$ values are obtained; a

typical example is menthol (**n**), showing a Δδ value of 1.69 ppm. The comparison, however, between the more bulky 2-heptanol (**f**) and smaller 2-butanol (**m**) shows that the largest Δδ is obtained when the smallest alcohol is used (1.10 and 2.73 ppm, respectively). When amines are used, the substrates possessing an aromatic ring system give the largest diastereomeric shift differences Δδ, as can be clearly seen when α-phenylethylamine (**l**) is compared with 2-aminobutane (**k**) with Δδ values of 2.46 ppm and 0.26 ppm respectively. The situation is not so clear when α-thiol acids or their ester derivatives are used. Sometimes the largest Δδ value is found for the free acid, as for **p** with Δδ 2.30 ppm compared to 0.23 ppm for the ester derivative (**q**). On the other hand, the ester derivative **3.14** (**s**) gives the largest Δδ value (1.09 ppm) as compared to the free acid **r** (0.19 ppm). Although reagent **3.12** is more reluctant towards moisture than the reagents **3.5**, **3.6** and **3.7**, described by Alexakis and co-workers[6], water can act as a nucleophile to give reaction to **3.18**.

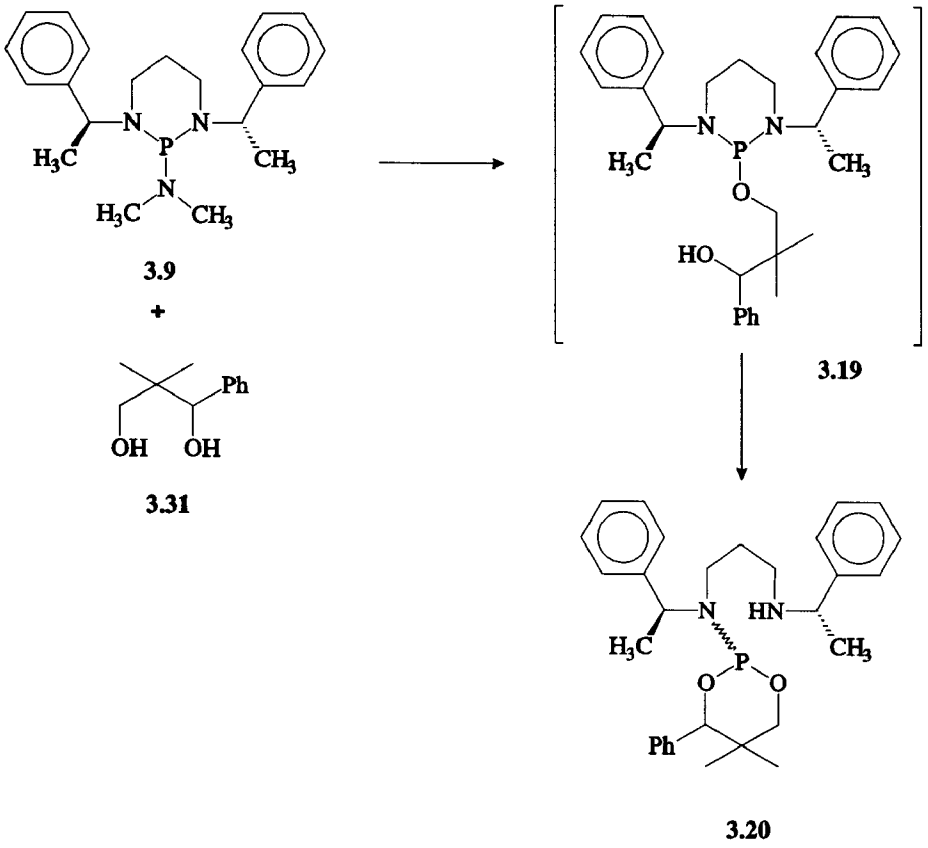


3.12 **3.17** **3.18**

Scheme 3.8 Reaction of reagent 3.12 with H_2O to 3.18

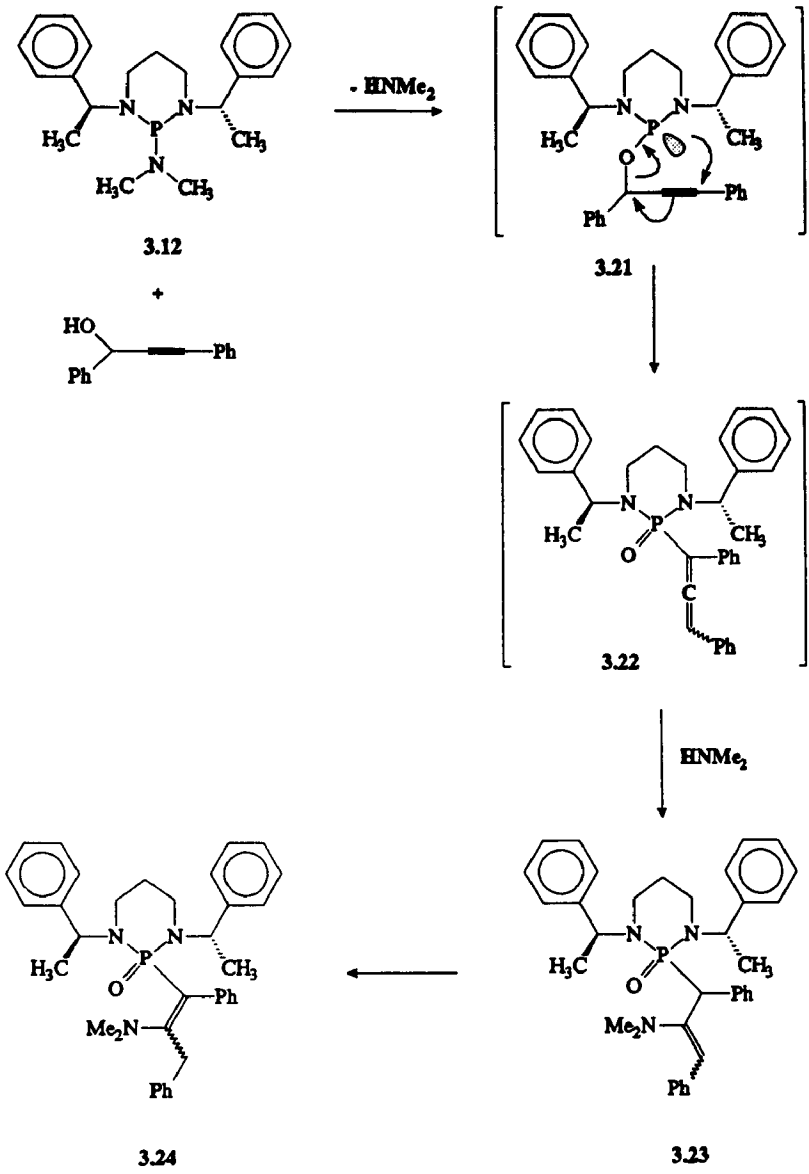
The rate of this reaction appears to be strongly dependent upon the amount of moisture present (Scheme **3.8**). When reactive alcohols or amines are used as nucleophiles in the presence of H_2O, it is possible to react them with reagent **3.12**, suppressing the side reaction with water to about 10-15%, without disturbance of the actual determination of the enantiomeric ratios.

We have also screened the applicability of the diazaphosphorinane **3.18** formed, in the enantiomeric excess determination. It appeared not to be of use because of decomposition under the conditions as needed (see Chapter 4 for the details).
Another drawback is encountered when diols are used as substrates. A cyclization reaction to the corresponding dioxaphospholane system **3.20** is observed, as depicted in Scheme **3.9** using *e.g.* phencydiol[14] **3.31** as the substrate (see also Chapter 4). Upon cleavage of the diazaphospholane ring moiety of **3.19**, the phosphorus atom in **3.20** becomes chiral and a number of signals, beside the signals belonging to the diastereomeric adducts, appear in the decoupled ^{31}P NMR spectrum.



Scheme 3.9 Reaction of 3.31 with reagent 3.12 to dioxaphospholane 3.20

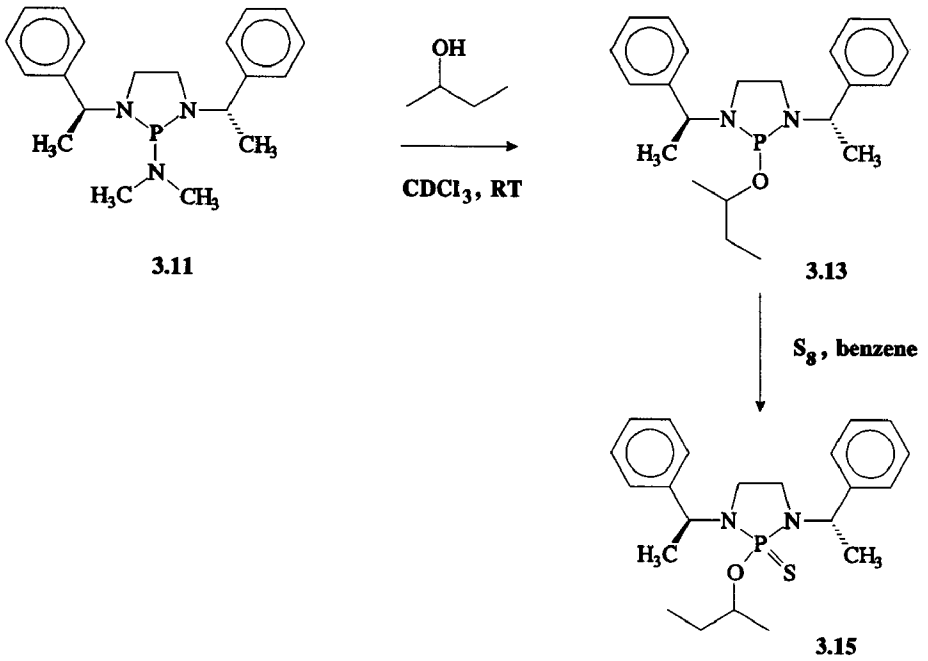
When propargylic alcohols, like in entry **g** (Table **3.1**), are used, a rapid [2,3]-sigmatropic rearrangement takes place[15,6] (Scheme **3.10**). This rearrangement appears to be so fast that the signals belonging to the initially formed products are not always observed. Although this type of rearrangement is known to occur with complete stereocontrol, the subsequent attack of the eliminated dimethylamine on the allene system of **3.22** ultimately gave enamine[16] **3.24**, therefore no information was obtained about the enantiomeric



Scheme 3.10 Proposed mechanism[6,15] for the [2,3]–sigmatropic rearrangement of propargylic alcohol and 3.12 (g in Table 3.1)

composition of propargylic alcohols by using this technique.
The results obtained with derivatizing agent **3.11** for enantiomeric excess determinations (Scheme **3.11**) are collected in Table **3.2**, the indices again referring to Scheme **3.7**.

The chemical shift differences Δδ (^{31}P NMR) as obtained using reagent **3.11** are smaller than the values as obtained using reagent **3.12**, although an interesting comparison can be made.



3.11 **3.13** **3.15**

Scheme 3.11 *Reaction of **3.11** with racemic sec-butanol. Subsequent reaction with S_8 transforms compound **3.13** into thiophosphoramidate **3.15***

When racemic alcohols are used as substrates, alcohols containing an aromatic ring (substrates **a** and **e**), typically give rather small Δδ values of 0.20 ppm and 0.39 ppm, respectively, when compared with the other alcohols, like **c** and **f**, which give much higher Δδ values, in the range from 1.05 ppm (**c**) to 1.98 ppm (**f**). This trend, however, is not so obvious as for reagent **3.12** , which shows an inversed shift dependency.

For amine containing substrates also, the observed shift differences appear to be larger for the alkyl amines when compared to the aromatic ring substituted counterparts. The largest Δδ value is found for 2-aminobutane (**k**, 5.21 ppm), while α-phenylethylamine (**l**) only gave a Δδ value of 0.15 ppm. Again, this trend seems to be the reverse of the shift behaviour of reagent **3.12**, showing the largest shift differences for α-phenylethylamine (**l**, 2.46 ppm) and the smallest for 2-aminobutane (**k**, 0.26 ppm).

Interesting is the behavior of reagent **3.11** in the analysis of free α-thiol acids (**p** and **r**), showing reaction with the thiol group as well as with the free acid group. The signals located at δ 136.51 and 134.29 ppm belong to the thiol derivatized product, whereas the acid derivatized product shows signals at δ 133.48 and 128.87 ppm. The calculated enantiomeric ratios, however, are in good agreement with each other, indicating that although two different competitive types of reaction are taking place at the same time

Substrate	δ (ppm)	Δδ (ppm)	ratio
d,l-Phe	96.91	0.49	49.5:50.5
d,l-Ala	96.99	0.45	49.5:50.5
d,l-PG[a]	122.51	0.19	49.5:50.5
e	124.08	0.39	49:51
c	125.34	1.05	49.5:50.5
f	125.00	1.98	49.5:50.5
a	124.15	0.20	49:51
g	114.20	5.21	49.5:50.5
l	94.36	0.15	50:50
k	94.61	5.21	50:50
d,l-heptylamine	93.68	0.29	49.6:50.4
t	123.89	0.08	49.1:50.9
r[c]	136.51	1.21	48.5:51.5[b]
	133.48	0.75	50:50
p[c]	134.29	0.68	43:57[b]
	128.87	0.53	44:56
s	136.84	0.56	50:50
q[c]	135.63	0.54	44:56

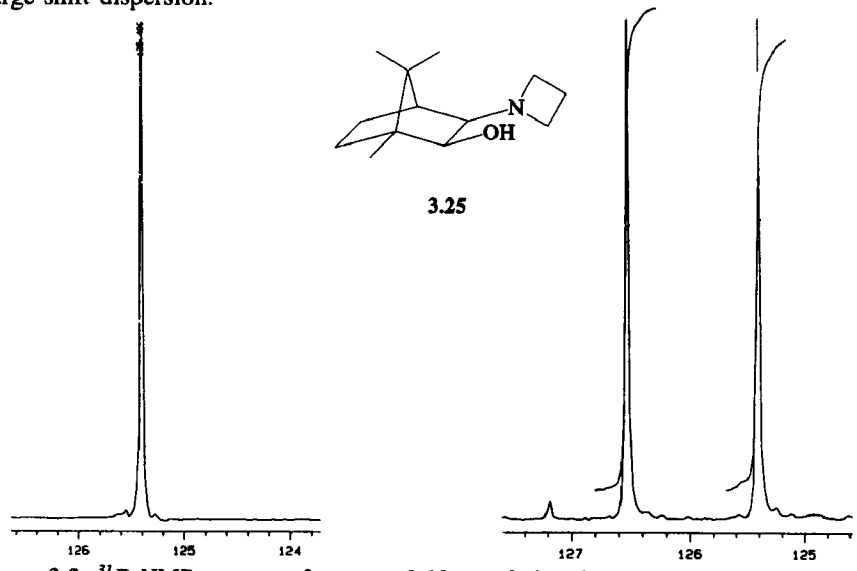
Table 3.2 *^{31}P NMR data of derivatives of **3.11** and racemic amines, alcohols, amino acids, α-thiol acids and α-thiol acid esters recorded in $CDCl_3$ [L]= 0.1 M.*
a) PG is Phenylglycine.
b) The additional absorption is due to P-O bond formation, see text for explanation.
c) Enantiomerically enriched product was used.

kinetic resolution is not likely to be of any importance.
Thus, when reagents **3.11** and **3.12** are compared, the difference in chemical shift differences ΔΔδ, appears to be sensitive not only to steric factors, but also to stereo-electronic and (ring) conformational effects. Similar behavior is also observed with a *series of substrates* and the reagents **3.11** or **3.12**.
In Chapter 6 the relationship between the induced chemical shift differences Δδ and geometry will be discussed in greater detail.

The side reactions as described for reagent **3.12** can also take place when **3.11** is used, although this reagent seems to be more sensitive towards moisture. In fact, reagent **3.11** shows a lesser selective reactivity, as compared to reagent **3.12** over the entire range of substrates used. Several free amino acids, however, were analyzed using these reagents under phase transfer conditions (solid-liquid phase). Both reagents are not reluctant towards traces of water in the reaction medium or ultimately towards water as the solvent itself, although both are more stable towards moisture than the reagents as reported by Alexakis and co-workers[5,6].

3.2.3 *Spectroscopic and conformational study of diastereomeric products of reagents 3.11 and 3.12*

As was already stated before, reagents **3.11** and **3.12**, and more so the diastereomeric products **3.13** and **3.14**, show rather complex spectral behavior in the ^{1}H NMR, due to the addopted conformations and excessive H-H and P-H coupling. Although it is possible to obtain the diastereomeric ratios from the ^{1}H NMR data, the use of ^{31}P NMR techniques is far superior, giving only two nicely separated signals for the diastereomeric products with a large shift dispersion.



3.25

Figure 3.3 ^{31}P NMR spectra of reagent 3.12 coupled with racemic and enantiomerically pure 3.25

In Figure **3.3**, the decoupled ^{31}P NMR spectra of the products of **3.12** and racemic (a) and enantiomerically pure (-)-*cis*-exo-3-(1-azetidinyl)isoborneol **3.25** (b) are given, recorded in $CDCl_3$ [L]= 0.1 M. As can be seen, the diastereomeric ratio is readily obtained from the

integration of both signals: the absence of the second signal in (*b*) indicates that the material used is enantiomerically pure[#] within the error limits of the NMR technique[##].
When racemic α-phenylethylalcohol is coupled to reagent **3.12** (**a**, Table **3.1**), the diastereomeric shift differences Δδ are not only seen in the decoupled ^{31}P NMR spectrum (Δδ 1.38 ppm), but also in the ^{1}H NMR, allowing not only the analysis of the diastereomeric ratio but also providing a tool to gather more information about the conformational behavior of the diastereomeric adducts (Figure **3.4**).

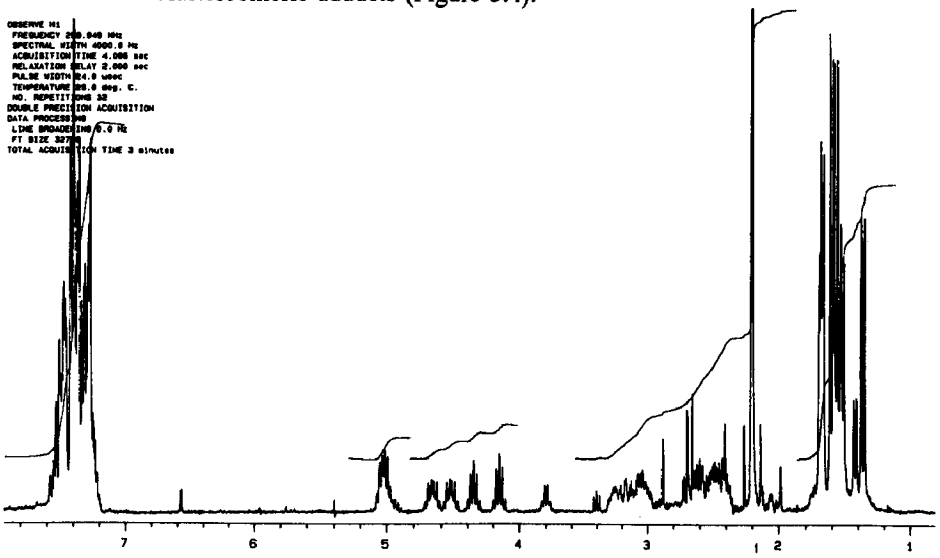


Figure 3.4 *^{1}H NMR spectrum of the diastereomeric product **3.14** using racemic α-phenylethylalcohol (**a**, Table **3.1**) recorded in $CDCl_3$ [L]= 0.1 M*

The crude spectrum of **3.14a** shows a complex pattern of six multiplets with a ^{3}J coupling, due to the α proton of the alcohol moiety, and a $^{4}J_{PH}$ coupling arising from the phosphorus nucleus, located between δ 1.37–1.69 ppm, all belonging to the three methyl groups. The protons $\underline{4}^{ax}$ and $\underline{4}^{eq}$ of both diastereomers (***A*** and ***B***) of **3.14a** are also located in this area (δ 1.80 ppm), as can be seen from the COSY spectrum (Figure **3.5**). The protons $\underline{3}^{ax}$, $\underline{3}^{eq}$, $\underline{5}^{ax}$ and $\underline{5}^{eq}$ of both diastereomers are situated in the range δ 2.40–3.35 ppm, and can only be fully assigned on the basis of the 2D COSY spectrum and the coupling constants. The axial protons $\underline{3}$ and $\underline{5}$ are located at δ 2.41 and δ 2.58 ppm for diastereomer ***A*** and at δ 2.50 and δ 2.63 ppm for diastereomer ***B***. For diastereomer ***A*** the equatorial protons $\underline{3}$ and $\underline{5}$ are located at δ 3.10 and δ 3.29 ppm, whereas the resonances belonging to diastereomer ***B*** are assigned resonating at δ 3.04 and δ 3.21 ppm, respectively.

[#] Both the racemic and the enantiomerically pure substrates were synthesized by Drs Andre de Vries, the experimental details will be part of his forthcoming thesis.

[##] For a short discussion about the error limits of NMR compared to GC and HPLC techniques see; Schurig, V., *Kontakte (Darmstadt)* **1985**, *2*, 22; **1986**, *1*, 3.

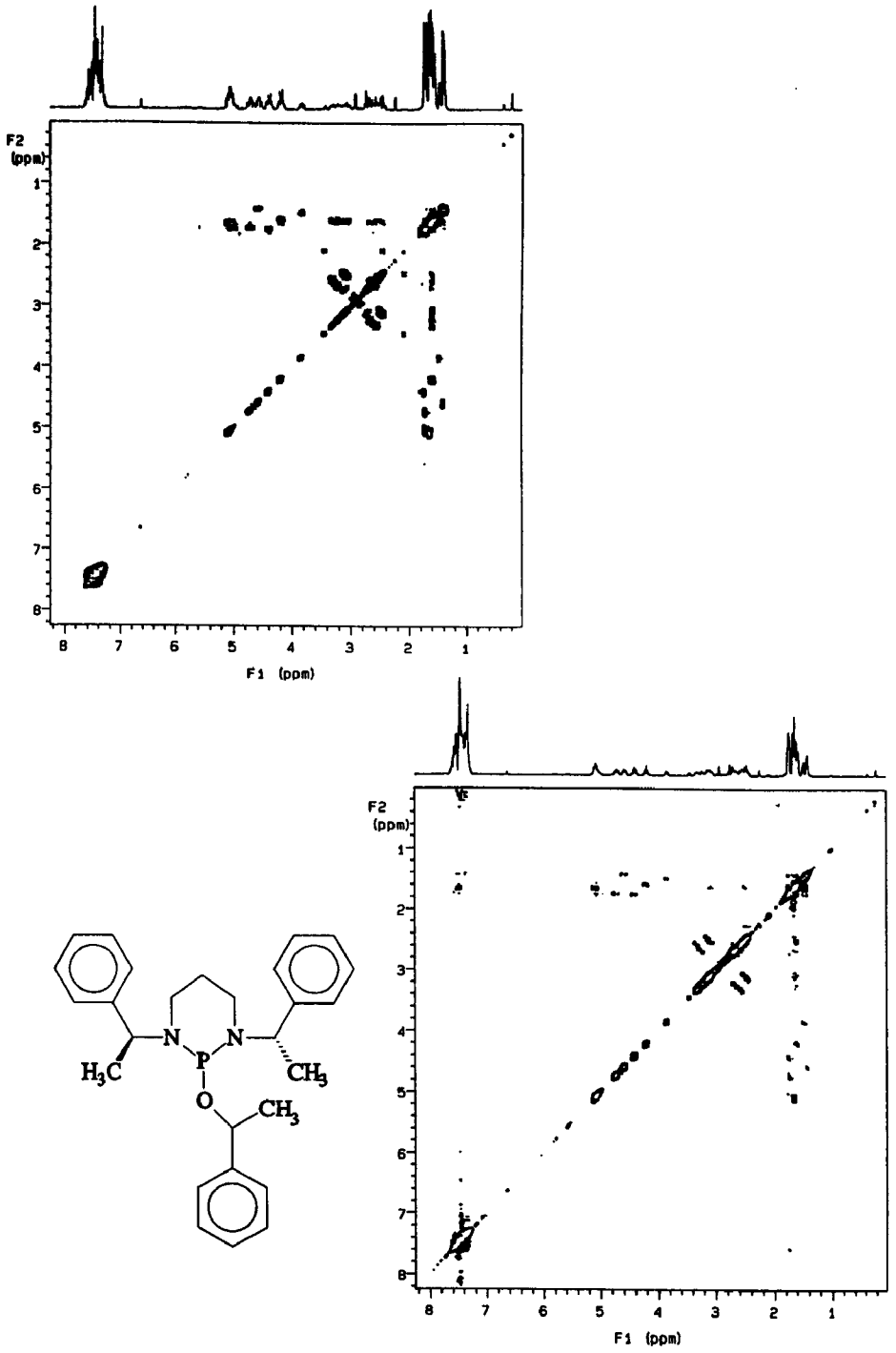


Figure 3.5 COSY and NOESY spectra of product 3.14 using racemic α-phenyl-ethanol (a) recorded in $CDCl_3$ [L]= 0.1 M

The most striking diastereomeric shift differences, however, are observed in the exocyclic part of the molecule. The protons 2 and 6 belonging to diastereomer *A* resonate at δ 4.20 and at δ 4.58 ppm respectively, whereas the same protons in diastereomer *B* are shifted to δ 4.40 and δ 4.66 ppm. Surprisingly, the α proton of the substituted alcohols hardly shows any diastereomeric shift dispersion; both show absorptions at δ 5.01 and δ 5.09 ppm. The large signal at δ 2.20 ppm belongs to the liberated dimethylamine, which does not interfere with the enantiomeric excess determination itself.

From the NOESY spectrum the interaction between the α proton of the substituted alcohol and proton 3^{ax} (diastereomer *B*) are clearly seen, probably due to the π–stacking of the three aromatic ring systems. This *normally* rather sterically hindered conformation brings the α proton in the vicinity of the axial proton at position 3. This would mean that the alcohol moiety posseses the axial position on phosphorus, since this is the only possible way for the system to give an interaction of the α proton with either one of the axial ring protons. Clearly, this substitution at the phosphorus center proceeds with inversion of configuration with respect to the NMe_2 and free electron pair on the phosphorus nucleus of reagent **3.12**. The rather large diastereomeric shift dispersion when using aromatic alcohols or amines as the substrates, could very well be the result of the π–π stacking ability. Rather severe conformational changes are necessary to bring the aromatic systems in the desired positions.

Strangely enough, no *special* NOESY signals[#] were found for diastereomer *A*. Based upon the data from the NOESY spectrum and measurements using enantiomerically pure (*S*)–α–phenylethylalcohol (not shown), it was concluded that diastereomer *B* must be the product of reagent **3.12** and (*S*)–α–phenylethylalcohol.

For diastereomeric products of reagent **3.11**, the observed chemical shift dispersion in the ^1H NMR is much smaller. When α–phenylethanol is coupled to reagent **3.11** the observed diastereomeric shift difference in the decoupled ^{31}P NMR (δ 0.20 ppm) is much smaller compared to the same adduct with reagent **3.12**. Using NOESY techniques, no signs of interaction between the coupled alcohol moiety and the five membered ring was found for either of the diastereomers. This strongly suggests that the π–π stacking as proposed for the adducts of reagent **3.12**, is of no importance here, leaving the alcohol moiety in the equatorial or at least strongly distorted axial position with no possibility to give an interaction with any of the protons belonging to the five ring system.

Also when alcohols that do not contain aromatic rings are coupled to reagents **3.11** or **3.12** interactions of interest are not observed in the NOESY spectra.

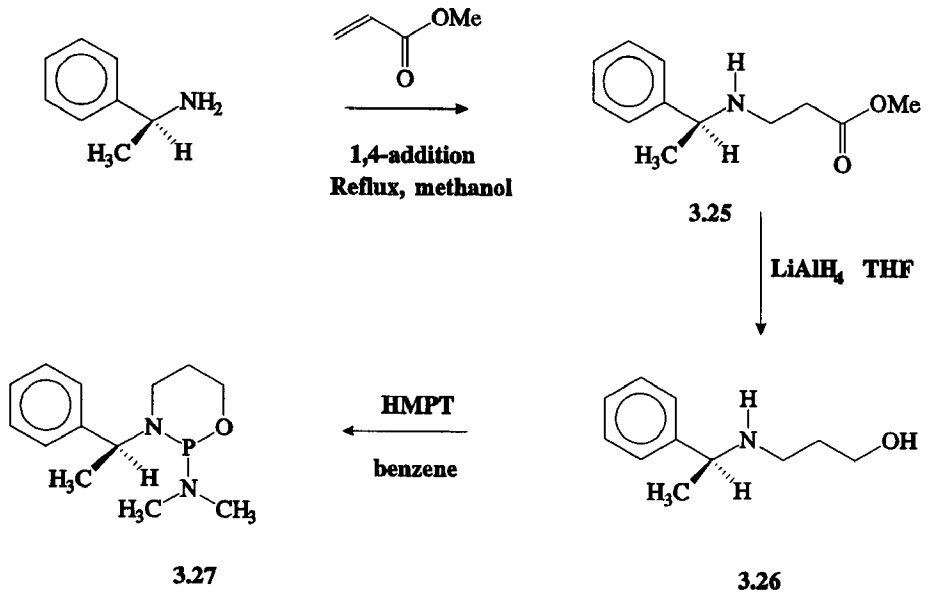
It should be noted, however, that the chemical shift is not only a function of structural variations like bond angles and lengths, but also of factors like electronegativity of the phosphorus nucleus and the substituents[11,17]. It is clear that all these factors together play a role here, the overall effect resulting in the observed chemical shift dispersion.

[#] Except for the NOESY interactions that were expected, like the interactions of the ring protons with each other very little NOE's were observed, which we not anticipated on the basis of the steric effects noted above.

In Chapter 6, the correlation between structural factors and chemical shift of penta-coordinated phosphorus will be discussed in greater detail.

3.2.4 *Other trivalent phosphorus containing reagents for the enantiomeric excess determination*

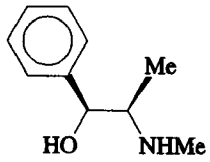
As was already mentioned in Chapter 3.2.2 and shown in Schemes **3.8** and **3.9**, phosphorus shows great preference for being substituted with oxygen (trivalent phosphorus containing compounds are in fact easily oxidized into a pentavalent moiety[18]).
We therefore developed several cyclic chiral, trivalent phosphorus derivatives which bear one or two oxygen phosphorus bonds in the ring, expecting that these systems would show a higher tolerance towards water, and show a higher selectivity towards reaction with nucleophiles. For the comparison purpose, one of the amino alcohols (**3.26**) used contains a α-phenylethylamine unit, as is shown in Scheme **3.12**. Treatment of methylacrylate with (*S*)-α-phenylethylamine easily yields the methyl-3-*N*-(1-(*S*)-phenylethyl)aminopropionate **3.25** in 93% yield, which was subsequently reduced with $LiAlH_4$ to amino alcohol **3.26** in 64% yield after a Soxhlet extraction of the lithium salts[12,19]. Amino alcohol **3.26** was also obtained by means of a nucleophilic substitution reaction using 3-chloropropanol and (*S*)-α-phenylethylamine without solvent[12].



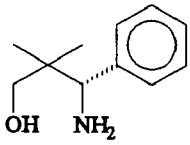
Scheme 3.12 Synthesis of product 3.27

The enantiomeric purity of **3.26** was checked using the methodology described in Chapter 4[20], which indicated that no racemization had taken place.

The reaction of **3.26** with HMPT in dry benzene, however, yielded a mixture of products, containing the two expected diastereomers of **3.27** (Note that in **3.27**, the phosphorus atom is chiral). Based upon ^{31}P NMR data of the crude mixture, it is clear that also *bis* and even *tris* oxygen substituted phosphorus derivatives and elimination products were formed, although product **3.27** is the main product (yield 65%). It appears that reaction with alcohols proceeds more readily than the desired intramolecular reaction. Attempts to separate and purify the products by distillation resulted in *violent explosions*. Column chromatography also, was not successful and gave rise to decomposition of all materials.



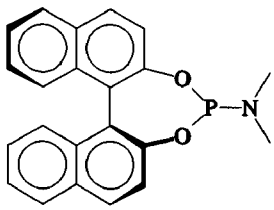
3.28



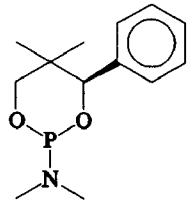
3.29

Scheme 3.13 Two amino alcohols that were not successfully derivatized with HMPT

When other amino alcohols, like ephedrine **3.28** and amino alcohol **3.29**, were used in the reaction with HMPT, the same kind of problems were faced (Scheme **3.13**).
It became obvious that, when the crude mixtures of derivatives **3.28** or **3.29** were allowed to react with racemic alcohols like *e.g.* α-phenylethanol, diastereomeric products were formed showing large shift dispersion Δδ, although the obtained results were not of direct use for analytical purposes, due to the problems already mentioned.



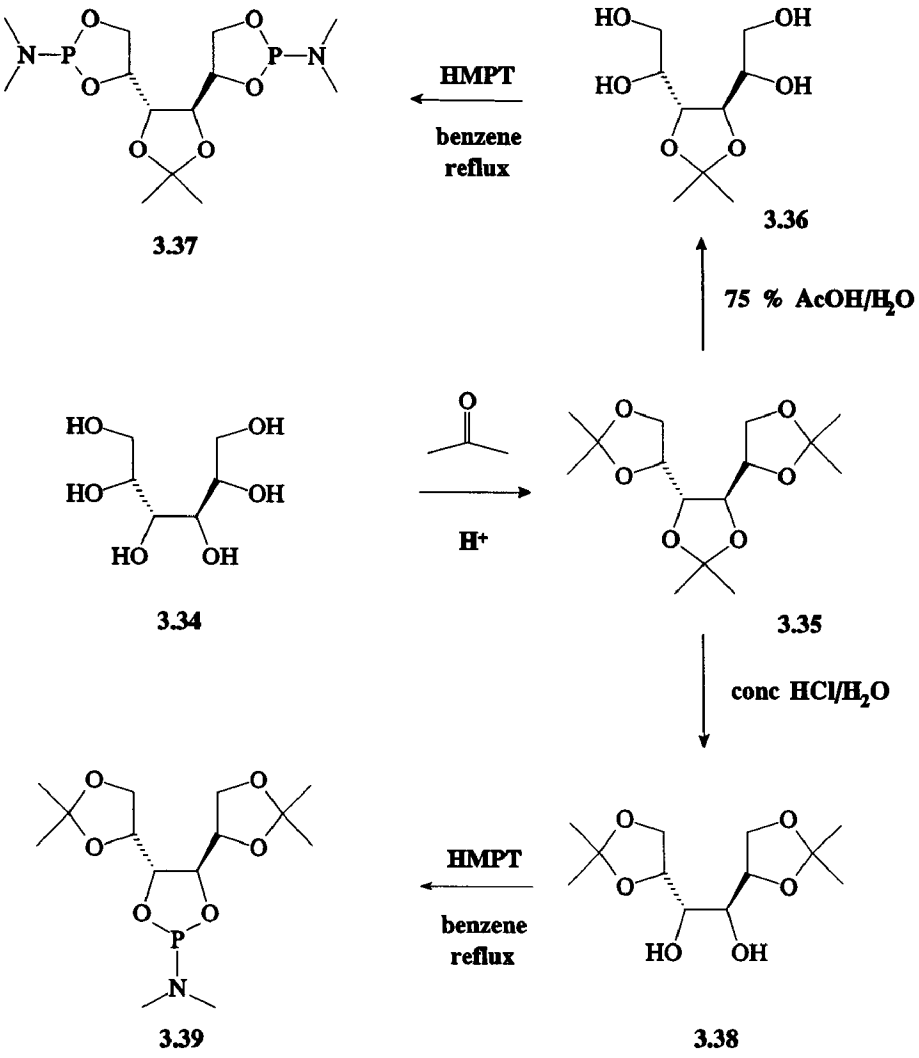
3.32



3.33

Scheme 3.14 Dioxophospholidines based upon easily available diols

Being aware of the synthetic problems that arise when trivalent phosphorus reagents like HMPT are coupled to amino alcohols, we decided to use chiral diols as ligands. Readily available diols, like (+)-bis-ß-naphthol **3.30** (not shown) and (*R*)-phencydiol **3.31** (Scheme **3.9**) were functionalized with HMPT by reflux in dry benzene, yielding the trivalent phosphoric products **3.32** and **3.33** in nearly quantitative yield (Scheme **3.14**).



Scheme 3.15 Trivalent derivatizing agents based upon mannitol

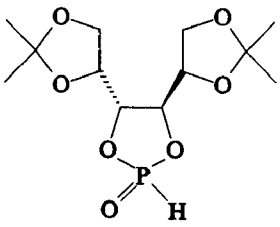
In the case of **3.33**, two diastereomers were obtained, which could not be separated, although the ^{31}P NMR signals were so far apart ($\Delta\delta$ 37.12 ppm), that use as an *e.e.* determining agent might be possible. These materials appeared to be stable towards moisture and oxygen. In fact these materials do not react with alcohols, amines or water under the employed conditions. Also, when more drastic conditions were employed, like

the use of bases (Et_3N, NaH, NaOH or n-butyllithium#) to enhance the nucleophilicity of the substrates, no reaction was achieved.

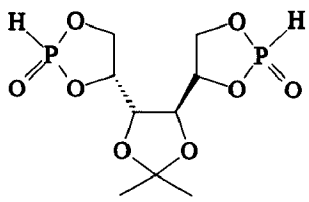
Another approach was based upon the use of trivalent phosphorus containing *sugar-like* derivatives. These ligands are capable of forming strong complexes with water when functionalized with pentavalent phosphorus, as became obvious in the course of the work described in the Chapters 4 and 5. In fact, we have synthesized these (tri or pentavalent) systems to investigate their possible behavior as cell-membrane mimics[22b], as well as possible *e.e.* determining agents. Using mannitol **3.34** as the sugar building block, trivalent phosphorus derivatives **3.37** and **3.39** were synthesized according to Scheme **3.15**.

First, *D*-mannitol was functionalized with acetone giving 1,2-3,4-5,6-O-tri-iso-propylidene-*D*-mannitol **3.35** in 70% yield[21]. Subsequent selective hydrolysis using aqueous acetic acid, yielded the tetra alcohol 3,4-O-isopropylidene-*D*-mannitol **3.36** in 80%[22]. Reaction with HMPT afforded the bis-dioxophospholidene **3.37** in 93% yield as a white, air and moisture stable, solid material.

From **3.35** the 1,2-5,6-di-O-isopropylidene-*D*-mannitol **3.38** was also easily available (61%)[23], which was subsequently converted into the desired dioxophospholidine **3.39** in 86% yield. As with **3.37**, this material was an air and moisture stable white solid. Adduct **3.37** appears to be enantiomerically pure with respect to the phosphorus nuclei, which is surprising when compared to the HMPT derivatives of the amino alcohols mentioned earlier.



3.40



3.41

Scheme 3.16 Formation of pentavalent phosphites from trivalent phospholidines

As with derivatives **3.32** and **3.33**, however, reagents **3.37** and **3.39** did not show any reactivity towards alcohols or amines, regardless the conditions used, including the use of bases (NaH, Et_3N) to enhance the nucleophilicity of the substrates. Both derivatives reacted with one or two equivalents of water, respectively, under controlled conditions, yielding pentavalent phosphorinanes **3.40** and **3.41** in 90-95% yield (Scheme **3.17**). The

When n-butyllithium is used as a base, decomposition took place resulting in the liberation of the free diols. Unpublished results, Drs Thijs Stock.

use of the phosphorinanes in the enantiomeric excess determination is described in detail in Chapter 4, although the results using them as e.e. determining agents were not hopeful. Again, as with the other oxygen containing phospholidines, the observed reactivity is too low for reaction with alcohols and amines, regardless their structure. This implies that these compounds are not useful as *e.e.* determining agents.

3.3 *Conclusions*

In Chapter 3 the successful synthesis of two, trivalent phosphorus containing chiral derivatizing agents, as well as their use as agent for the enantiomeric excess determination is described. The described compounds **3.11** and **3.12** are not the first of this type, since Alexakis and co-workers developed several trivalent phosphorus based derivatizing agents[5,6]. However, the synthetic availability and stability of the in this Chapter described compounds is striking when compared with those previously reported. The amines used by Alexakis, chiral cyclic diamines, are rather expensive and only available after much synthetic work. Furthermore, the trivalent phosphorus containing agents appear not to be stable towards moisture. The systems described in this chapter are easily available and are based upon cheap α-phenylethylamine. After derivatization with HMPT, the trivalent phosphorus containing derivatives appear to be reasonable stable towards moisture; it is even possible to react them with alcohols in the presence of traces water, provided that reactive alcohols or amines are used.
Several types of substrates are derivatized and the enantiomeric excess of alcohols, amines, amino alcohols, α-thiol acids and several amino acids can be determined easily. The diastereomeric shift differences are usually large when ^{31}P NMR techniques are used. Besides ^{31}P NMR techniques, ^{1}H NMR can also be applied sometimes. Studies based upon the use of 2D NMR techniques were performed in the hope to gather insight in the factors that govern the diastereomeric shift differences as a function of the intrinsic conformational parameters. Although not very successful, these results were useful in the modelling studies as described in Chapter 6.
Several other derivatizing agents based upon trivalent phosphorus were developed in order to reduce the reactivity towards (traces) water. This resulted in derivatives that showed in fact too little reactivity to be used as derivatizing agents in the enantiomeric excess determination. The newly synthesized compounds form, however, an interesting new class of molecules.

3.4 *Experimental*

For general remarks, see Chapter 2.5. Due to purification problems, not all the trivalent phosphorus derivatives could be fully characterized.

N,N'-bis(1-(S)-Phenylethyl)-1,2-ethylenediamine (3.9)[12]
(*S*)-α-Phenylethylamine (72.0 g, 0.59 mol) was heated to 100 °C and 1,2-dichloroethane (22.5 g, 0.23 mol) was added to the stirred solution over 2 h. Stirring of the mixture was continued for 16 h at 100 °C. The mixture was cooled to 60 °C and 150 mL of a saturated

KOH solution in water was added with continued stirring. After cooling to room temperature, the mixture was extracted three times with 150 mL of CH_2Cl_2. The combined organic layers were washed with brine and dried (Na_2SO_4). After removal of the solvent unreacted (*S*)–α–phenylethylamine was removed by vacuum distillation. The product was distilled (149–150 °C, 0.5 mm Hg)(lit[12] 110 °C, 0.02 mm Hg), yielding a colorless oil. Yield 37.5 g (0.15 mol, 62%). $[\alpha]_D^{20}$= –69.4° (c 1.10, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.35 (d, ^{3}J= 7.45 Hz, 6H), 1.50 (s, br, 2H), 2.54 (m, 4H), 3.65 (q, ^{3}J= 7.45 Hz, 2H), 7.20–7.41 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 24.31 (CH_3), 47.22 (CH_2) 58.01 (CH), 126.40 (CH), 126.58 (CH), 127.99 (CH), 145.71 (C); HRMS calcd 268.194, found 268.193.

N,N'–bis(1–(S)–Phenylethyl)–1,3–propylenediamine (3.10)[12]

This compound was prepared using the procedure as described for **3.9** from 43.6 g (0.36 mol) (*S*)–α–phenylethylamine and 25.0 g (0.12 mol) of 1,3–dibromopropane. The product was distilled at 148–151 °C, 0.01 mm Hg (lit[12] 115 °C, 0.02 mm Hg) to yield a colorless oil (28.6 g, 0.10 mol, 84%). $[\alpha]_D^{20}$= –66.3° (c 0.55, $CHCl_3$)(lit[12] $[\alpha]_D^{20}$= –66.4°); ^{1}H NMR ($CDCl_3$): δ 1.38 (d, ^{3}J= 6.65 Hz, 6 H), 1.43 (s, br, 2H), 1.62 (m, 2H), 2.52 (m, 2H), 3.78 (q, ^{3}J= 6.65 Hz, 2H), 7.21–7.40 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 24.28 (CH_3), 30.28 (CH_2), 46.32 (CH_2), 58.30 (CH), 126,42 (CH), 126.66 (CH), 128.31 (CH), 145.68 (C); HRMS calcd 282.210, found 282.210.

N,N'–bis(1–(S)–Phenylethyl)–1,2–ethylenediamino–N,N'–diaza–N'',N''–dimethyl–phospholidine (3.11)

A mixture of bisamine **3.9** (2.50 g, 9.33 mmole), hexamethylphosphorus triamide (3.05 g, 18.7 mmole) and a catalytic amount of dry NH_4Cl was gently refluxed in 50 mL of dry benzene for 96 h. During the reaction a stream of N_2 was passed through the flask in order to remove the formed dimethylamine. Benzene and excess $P(NMe_2)_3$ were removed under vacuum (0.01 mm) at 50 °C. The resulting oil was purified by chromatography over Al_2O_3 (benzene) and used as such. *Attempts to distill the products were not successful, and sometimes resulted in violent explosions.* The product appeared to be over 98% pure, based upon ^{31}P and ^{1}H NMR data. Yield 2.86 g (8.40 mmole, 90 %), colorless oil.
^{1}H NMR (C_6D_6): δ 1.55 (d, ^{3}J= 7.20 Hz, 3H), 1.58 (d, ^{3}J= 7.18 Hz, 3H), 2.54 (d, $^3J_{PH}$= 9.00 Hz, 6H), 2.62 (m, 1H), 2.76 (m, 1H), 3.02 (m, 1H), 3.09 (m, 1H), 4.18 (dq, $^3J_{PH}$= 7.15 Hz, ^{3}J= 7.20 Hz, 1H), 4.23 (dq, $^3J_{PH}$= 7.15 Hz, ^{3}J= 7.18 Hz, 1H), 7.18–7.39 (m, 10H); ^{13}C NMR (C_6D_6): δ 21.34 (d, $^3J_{PC}$= 13.10 Hz, CH_3), 21.91 (d, $^3J_{PC}$= 12.09 Hz, CH_3), 37.13 (d, $^3J_{PC}$= 17.21 Hz, CH_3), 46.82 (d, $^2J_{PC}$= 7.05 Hz, CH_2), 47.13 (d, $^2J_{PC}$= 8.18 Hz, CH_2), 56.76 (d, $^2J_{PC}$= 22.16 Hz, CH), 57.12 (d, $^2J_{PC}$= 18.13 Hz, CH), 126.65 (CH), 126.69 (CH), 127.42 (CH), 127.93 (CH), 128.03 (CH), 128.03 (CH), 128.33 (CH), 145.29 (d, $^3J_{PC}$= 5.02 Hz, C), 145.43 (d, $^3J_{PC}$= 5.03 Hz, C); ^{31}P NMR (C_6D_6): δ 105.62; HRMS calcd 341.202, found 341.202.

N,N'–bis(1–(S)–Phenylethyl)–1,3–propylenediamino–N,N'–diaza–N'',N''–dimethyl–phospholidine (3.12)

Prepared as described for **3.11**, using bisamine **3.10** (2.50 g, 8.86 mmole), yield 2.99 g (8.42 mmole, 95%). ^{1}H NMR (C_6D_6): δ 1.48 (d, ^{3}J= 6.05 Hz, 3H), 1.49 (m, *H4^{ax}*, 1H), 1.50 (d, ^{3}J= 5.90 Hz, 3H), 1.51 (m, *H4^{eq}*, 1H), 2.48 (d, $^3J_{PH}$= 9.05 Hz, 6H), 2.53 (m, *H3^{ax}*, 1H), 2.62 (m, *H5^{ax}*, 1H), 2.90 (m, *H3^{eq}*, 1H), 3.10 (m, *H5^{eq}*, 1H), 4.31 (dq, $^3J_{PH}$= 3.00 Hz, ^{3}J= 6.05 Hz, *H2*, 1H), 4.45 (dq, $^3J_{PH}$= 4.10 Hz, ^{3}J= 5.90 Hz, *H6*, 1H), 7.18–7.42 (m, *ArH*,

10H); ^{13}C NMR (C_6D_6): δ 17.87 (d, $^3J_{PC}$= 6.05 Hz, CH_3), 19.75 (d, $^3J_{PC}$= 13.09 Hz, CH_3), 26.66 (CH_2), 38.48 (d, $^2J_{PC}$= 18.13 Hz, CH_3), 38.97 (d, $^2J_{PC}$= 5.03 Hz, CH_2), 40.81 (d, $^2J_{PC}$= 3.02 Hz, CH_2), 58.14 (d, $^2J_{PC}$= 38.27 Hz, CH), 59.82 (d, $^2J_{PC}$= 35.26 Hz, CH), 126.36 (CH), 126.44 (CH), 127.24 (CH), 127.92 (CH), 127.96 (CH), 128.00 (CH), 144.63 (d, $^3J_{PC}$= 9.06 Hz, C), 145.15 (d, $^3J_{PC}$= 5.04 Hz, C); ^{31}P NMR (C_6D_6): δ 107.41; HRMS calcd 355.218, found 355.217.

Methyl-3-N-(1-(S)-phenylethyl)aminopropionate (3.25)

A solution of methylacrylate (50.0 g, 0.58 mol), (*S*)-α-phenylethylamine (54.5 g, 0.45 mol) and 250 mL of absolute methanol was heated to reflux for 12 h, and then concentrated. The remaining oil was directly distilled (bp 114–116 °C, 0.09 mm Hg), affording a colorless oil. Yield 80.7 g (0.39 mol, 86%). $[\alpha]_D^{20}$= −35.11° (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.26 (d, ^3J= 6.00 Hz, 3H), 1.62 (s, br, 1H), 2.40 (d, ^3J= 6.00 Hz, 1H), 2.41 (d, ^3J= 6.00 Hz, 1H), 2.64 (m, 2H), 3.57 (s, 3H), 3.71 (q, ^3J= 6.00 Hz, 1H), 7.18 (m, 1H), 7.22–7.27 (m, 4H); 24.15 (CH_3), 34.27 (CH_2), 42.51 (CH_2), 51.04 (CH), 57.77 (CH_3), 126.16 (CH), 126.50 (CH), 128.02 (CH), 145.16 (C), 172.80 (C); Analysis calcd for $C_{12}H_{17}NO_2$, C: 69.54, N: 6.76, H: 8.27. Found, C: 69.38, N: 6.71, H: 8.22; HRMS calcd 207.126, found 207.126

N-(1-(S)-Phenylethyl)aminopropanol (3.26)

A solution of **3.25** (25.0 g, 0.12 mol) in dry ether (100 mL) was added to a suspension of $LiAlH_4$ (9.61 g, 0.25 mol) in dry ether (100 mL). After heating under reflux for 6 h followed by stirring overnight at room temperature, water was added (10 mL), followed by 10 M NaOH solution (50 mL) and 5.0 g silicagel. The suspension was filtered over a P2 glass frit and the filtrate layers were separated. The ether layer was washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated to an oil which was distilled (105–106 °C, 0.05 mm Hg) to give **3.26**. Yield 16.7 g (93.02 mmole, 77%).
$[\alpha]_D^{20}$= −53.02° (c 0.19, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.30 (d, 3H), 1.61 (m, 2H), 2.57 (m, 1H), 2.63 (m, 1H), 3.61 (m, 2H), 3.63 (m, 1H), 7.10–7.30 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 23.80 (CH_3), 31.17 (CH_2), 46.86 (CH_2), 58.20 (CH), 63.09 (CH_2), 126.13 (CH), 126.68 (CH), 128.17 (CH), 144.61 (CH);; Analysis calcd for $C_{11}H_{17}NO$, C: 73.70, N: 7.81, H: 9.56. Found C: 73.55, N: 7.66, H: 9.48; HRMS calcd 179.131, found 179.131.

N-(1-(S)-Phenylethyl)aminopropanol (3.26)

Prepared as described for **3.9** from 3-chloropropanol (20.0 g, 213 mmole) and (*S*)-α-phenylethylamine (25.7 g, 213 mmole). Yield 41.4 g (200 mmole, 94%). Spectral data and purification as described above.

2,2'-O,O-(1,1'-Binaphthyl)-O,O'-dioxo-N,N-dimethyl-phospholidine (3.32)

(+)-bis-ß-Naphtol (2.00 g, 7.50 mmole), HMPT (1.40 g, 9.50 mmole), 0.01 g NH_4Cl and 10 mL of dry benzene were heated to reflux for 12 h. The mixture was concentrated under reduced pressure affording an oil. The oil was stirred with 25 mL of dry ether, upon which crystals were formed spontaneously. The crystals were recrystallized from dry ether. Yield 2.65 g (7.38 mmole, 98%). $[\alpha]_D^{20}$= 578.95° (c 0.06, $CHCl_3$); Mp 190–191 °C;
^1H NMR ($CDCl_3$): δ 2.75 (d, $^3J_{PH}$= 9.20 Hz, 6H), 7.25–7.55 (m, 8H), 7.91–8.00 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 35.81 (d, $^3J_{PC}$= 22.00 Hz, CH_3), 121.83 (d, $^3J_{PC}$= 1.01 Hz, CH), 123.02 (d, $^3J_{PC}$= 84.00 Hz, C), 124.53 (d, $^4J_{PC}$= 15.13 Hz, CH), 125.94 (s, CH), 126.78 (d, $^4J_{PC}$= 6.04 Hz, CH), 128.14 (d, $^7J_{PC}$= 6.01 Hz, CH), 130.01 (d, $^6J_{PC}$= 36.03 Hz, CH),

130.80 (d, $^4J_{PC}$= 47.38 Hz, C), 132.67 (d, $^3J_{PC}$= 2.01 Hz, C), 149.51 (d, $^2J_{PC}$= 38.31 Hz, C): ^{31}P NMR ($CDCl_3$): δ 148.72; Analysis calcd for $C_{22}H_{18}NO_2P$, C: 73.53, N: 3.90, P: 8.62, H: 5.05. Found C: 73.39, N: 3.74, P: 8.39, H: 4.97; HRMS calcd 359.107, found 359.108.

1,2-3,4-5,6-Tri-O-isopropylidene-D-mannitol (3.35)[21]

A suspension of *D*-mannitol (50.0 g, 0.27 mol), acetone (685 mL) and concentrated H_2SO_4 (6 mL) was stirred at room temperature. After stirring for 2 h the solution became clear and was stirred for another 8 h. Subsequently, the solution was diluted with H_2O (750 mL) upon which crystals formed spontaneously. The crystals were dried in vacuum at 50 °C and recrystallized from ethanol–H_2O, affording tiny white needles. Yield 57.38 g (0.19 mol, 70%). $[\alpha]_D^{20}$= 12.5° (c= 1.0, ethanol)(lit[21] $[\alpha]_D^{20}$= 12.5°, c= 1.0, ethanol);
Mp 69–70 °C (lit[21] 67–68 °C); ^{1}H NMR ($CDCl_3$): δ 1.26 (s, 6H), 1.31 (s, 6H), 1.32 (s, 6H), 3.98 (m, 2H), 4.11 (m, 2H), 4.2 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 25.16 (CH_3), 26.32 (CH_3), 27.26 (CH_3), 65.33 (C), 63.82 (CH_2), 69.61 (CH), 71.26 (CH), 108.70 (C); HRMS calcd 302.173, found 302.172.

3,4-O-Isopropylidene-D-mannitol (3.36)[21,22]

1,2–3,4–5,6–Tri–O–isopropylidene–*D*–mannitol **3.35**, (30.0 g, 99.3 mmole) was dissolved in 75% aqueous acetic acid (650 mL) and kept at 45 °C for 2 h. The solvent was removed at reduced pressure and twice co–evaporated with benzene. The obtained light yellowish oil was dissolved in acetone (1 L) and stirred with K_2CO_3 (30.0 g). Excess K_2CO_3 and mannitol were removed by filtration over a P4 glass frit. The filtrate was evaporated to yield an oil. The oil was dissolved in chloroform (250 mL) and stirred with 10.0 g of siligagel. After filtration, petroleum–ether 40–60 was added until **3.29** crystallized as white, very tiny crystals. Yield 17.32 g (79.44 mmole, 80%). $[\alpha]_D^{20}$= 29.61° (c 0.5, methanol); Mp 84–85 °C (lit[21,22] 85 °C); ^{1}H NMR (DMSO d_6): δ 1.28 (s, 6H), 3.31–3.40 (m, 2H), 3.41–3.62 (m, 4H), 3.79–3.91 (m, 2H), 4.50 (s, br, 2H), 5.15 (s, br, 2H); ^{13}C NMR (DMSO d_6): δ 27.24 (CH_3), 62.98 (CH_2), 72.88 (CH), 79.07 (CH), 108.28 (C); HRMS calcd 222.110, found 207.087 (– CH_3).

1,2-5,6-Di-O-isopropylidene-D-mannitol (3.38)[22]

A suspension of *D*–mannitol (200.0 g, 1.10 mol), acetone (4 L) and concentrated HCl (80 mL) was stirred for 4 h. The solution was neutralized with K_2CO_3 and concentrated to an yellowish oil. Subsequently, the oil was dissolved in 150 mL of boiling ethanol and filtered over a P4 glass frit. Upon cooling, tri–isopropylidene–*D*–mannitol **3.35** crystallized and was purified as described above. The filtrate was concentrated to a volume of 50 mL and stirred with hot water (150 mL) for 30 min. The remaining solution was filtered from traces of tri–isopropylidene–*D*–mannitol and refluxed in petroleum–ether 40–60 for 3 h. After the solution was cooled to room temperature, large lumps of crystalline material were obtained, which were crystallized from petroleum ether 40–60. The procedure was repeated twice, affording large needles.
Yield 16.6 g (63.7 mmole, 5.8%). $[\alpha]_D^{20}$= –0.6° !(c 0.2, water)(lit[22] $[\alpha]_D^{20}$= –0.5°, c 0.2, water); Mp 123–124 °C; ^{1}H NMR ($CDCl_3$): δ 1.45 (s, 6H), 1.51 (s, 6H), 2.78 (s, br, 2H), 3.85 (d, ^{3}J= 6.0 Hz, 2H), 3.92 (dd, $^2J_{AB}$= 8.4 Hz, ^{3}J= 4.6 Hz, 2H), 4.21 (dd, $^2J_{AB}$= 8.4 Hz, ^{3}J= 5.7 Hz, 2H), 4.24 (ddd, ^{3}J= 5.7 Hz, ^{3}J= 4.6 Hz, ^{3}J= 6.0 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 25.31 (CH_3), 27.51 (CH_3), 67.97 (CH_2), 72.00 (CH), 76.02 (CH), 110.01 (C); HRMS calcd 262.142, found 247.118 (– CH_3).

O,O-(1,2-5,6-Di-O',O''-isopropylidene-D-mannitol)-dioxo-N,N-dimethyl-phospholidine (3.39)

Prepared as described for **3.32** from **3.38** (2.00 g, 7.62 mmole) and HMPT (1.46 g, 9.00 mmole). Yield 2.49 g (7.45 mmole, 98%) white crystalline material. $[\alpha]_D^{20}$= 26.23° (c 0.04, $CHCl_3$); Mp 53-54 °C; ^{1}H NMR ($CDCl_3$): δ 1.36 (s, 6H), 1.40 (s, 3H), 1.42 (s, 3H), 2.59 (d, $^3J_{PH}$= 12.03 Hz, 6H), 3.70 (m, 1H), 3.88-4.02 (m's, 3H), 4.04-4.18 (m's, 3H), 4.20 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 25.62 (d, $^6J_{PC}$= 4.21 Hz, CH_3), 26.32 (d, $^6J_{PC}$= 2.33 Hz, CH_3), 32.43 (d, $^3J_{PC}$= 19.34 Hz, CH_3), 66.45 (d, $^4J_{PC}$= 105.06 Hz, CH_2), 74.39 (d, $^2J_{PC}$= 1.67 Hz, CH), 76.54 (d, $^3J_{PC}$= 33.12 Hz, CH), 118.56 (s, C); ^{31}P NMR ($CDCl_3$): δ 150.78; Analysis calcd for $C_{14}H_{26}NO_6P$, C: 50.14, N: 4.18, P: 9.24, H: 7.81. Found, C: 49.92, N: 4.06, P: 9.08, H: 7.76; HRMS calcd 335.150, found 335.150.

O,O'-(3,4-O''-Isopropylidene-D-mannitol)-bis-dioxo-bis(N,N-dimethyl)-phospholidine (3.37)

Prepared as described for **3.32** from **3.36** (2.50 g, 11.26 mmole) and HMPT (4.31 g, 26.60 mmole). Yield 2.63 g (7.09 mmole, 63%) white crystalline material. $[\alpha]_D^{20}$= 5.67° (c 0.05, $CHCl_3$); Mp 43-47 °C; ^{1}H NMR ($CDCl_3$): δ 1.14 (d, $^7J_{PH}$= 3.45 Hz, 3H), 1.16 (d, $^7J_{PH}$= 2.32 Hz, 3H), 2.24 (d, $^3J_{PH}$= 11.02 Hz, 6H), 2.83 (m, 2H), 2.45 (m, 4H), 2.78 (m, 2H); ^{13}C NMR ($CDCl_3$): due to excessive P-C coupling and relatively low stability in chloroform no good ^{13}C NMR spectrum could be obtained ; ^{31}P NMR ($CDCl_3$): δ 146.43; Analysis calcd for $C_{13}H_{26}N_2O_6P_2$, C: 42.39, N: 7.61, P: 16.82, H: 7.12. Found C: 42.27, N: 7.48, P: 16.68, H: 7.08; HRMS calcd 368.127, found 368.127

Typical procedure for the determination of the enantiomeric excess of alcohols, amines and thiols by the use of reagents 3.11 and 3.12

A solution of the substrate (0.1 mmole) and a slight excess (1.1 equivalent) reagent **3.11** or **3.12** in 1.5 mL of $CDCl_3$ or C_6D_6 is stirred at room temperature until dimethylamine is no longer evolved. This was checked with a pH indicator. Normally the reactions take about 1-8 h to be completed. Subsequent ^{31}P or ^{1}H NMR analysis affords the diastereomeric ratios immediately. The products can sometimes be purified by means of column chromatography over Al_2O_3 under a nitrogen atmosphere.

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